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09/192,167	11/13/1998	THOMAS J. MEADE	A-67412/RFT/	9443

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EXAMINER

CRANE, LAWRENCE E

ART UNIT

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/192,167	Applicant(s) Meade et al.	
	Examiner L. E. Crane	Group Art Unit 1623	

- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--3--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

Status

- ☒ Responsive to communication(s) filed on **-11/02/01 (amdt C)-**.
- ☒ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claims **--2-11 & 13-15--** are pending in the application. Claims **-[]-** have been cancelled.
- Of the above claim(s) **--[]--** is/are withdrawn from consideration.
- ☐ Claim(s) **--[]--** is/are allowed.
- ☒ Claims **--2-11 & 13-15--** are rejected.
- ☐ Claim(s) **--[]--** is/are objected to.
- ☐ Claim(s) **--[]--** are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on **-[]-** are ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on **-[]-** is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119(a)-(d)

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
- ☐ All ☐ Some ☐ None of the CERTIFIED copies of the priority documents have been received.
- ☐ received in Application No. (Series Code/Serial Number) **-[]-**.
- ☐ received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
- * Certified copies not received: **-[]-**.

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). **-[]-**
- ☒ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other: **-[]-**

U.S. Patent Trademark Office

Office Action Summary

PTO-326 (Rev. 06/19/01)
S. N. 09/192,167

Part of Paper No. **18**
Copy for ☒ FILE ☐ APPLICANT

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No claims have been cancelled, no new claims have been added, and claims 11 and 13-14 have been amended as per the amendment filed November 6, 2001.

Claims 2-11 and 13-15 remain in the case.

5 The disclosure is objected to because of the following informalities:

In the disclosure at page 16, "Structure 3" is missing hydrogens to complete two carboxyl groups.

10 In the disclosure at page 16, "Structure 4" the bottom two ethyl (?) phosphonic acid substituents are either unclear or incomplete. Did applicant intend -- $\text{CH}_3\text{-CH}_2\text{-P(=O)(OH)-}$...-- (lower left) and -- ... $\text{-P(=O)(OH)-CH}_2\text{-CH}_3$ -- (lower right), respectively?

Appropriate correction is required.

15 Claims 2-11 and 13-14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20 In claim 7 the term "comprising" (first and third occurrences only) is incorrect in the instant claim because said term implies that the chemical structure of the compound/substituent being claimed contains additional structural component(s) not defined in the claim. Applicant is respectfully requested to substitute narrow language such as -- consisting of -- or the like for the noted term. The same problem reoccurs in claims 2 and 3.

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Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

5 Applicant's arguments again miss the point. Applicant is referred to the comments following the enablement and art rejections. Narrow claims are all that are possibly allowable in the instant case. The comments in response from the previous Office action are repeated below.

Applicant's arguments filed April 19, 2001 have been fully considered but they are not persuasive.

10 Applicant argues that "comprising" is proper in all claims directed to all chemical compounds. Examiner respectfully disagrees. When the compounds (starting materials, intermediates and products) are each single molecules as herein, as opposed to a collection of polymeric chains of various lengths and monomer sequences then the term
15 "comprising" is incorrect because the metes and bounds of each compound are describable by a single chemical structure and, as herein, there is no good reason not to completely describe, by chemical name or chemical structure, each and every compound within the process. Applicant also argues that "it is the prior art that determines whether an
20 open ended term such as "comprising" is appropriate." Examiner respectfully disagrees. Applicant's argument oversimplifies the process of patent application claim examination, a process which relies on multiple parts of the U. S. Code and the Code of Federal Regulations to determine patentability and the absence thereof, including the
25 appropriateness of judicially recognized terms. Applicant also argues that the presence of the term "comprising" is justified by the presence in the disclosure of lists of compounds which may serve as "electron

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transfer moieties,” “compounds which contain primary amines,” and related process details. Examiner respectfully disagrees. As noted in the grounds of rejection functional terms of the kind quoted have meanings which may be read to include a vast array of subject matter not included within the disclosure and are therefore lacking in the degree of precision expected in view of 35 U.S.C. §112, second paragraph.

In claim 7, lines 6-8, the terms “cyclization agent” and “cyclized intermediate” are relatively meaningless unless the details of the chemical reaction being alluded to are provided, thereby rendering this portion of the instant claim lacking in adequately defined metes and bounds.

Applicant’s arguments filed November 6, 2001 have been fully considered but they are not persuasive.

The only area of the instant disclosure wherein the instant noted terms have meaning is in the structures of Figures 1-3. Applicant is again respectfully requested to use chemical structures to define the instant process, preferably defining the whole process of Figure 3 in claim 7.

In claim 2, adding a phosphoramidite moiety to a nucleoside is possible, but how such a group is being added in this case remains unclear because of the lack of definiteness found in claims 7 and 2.

Applicant’s arguments filed November 6,, 2001 have been fully considered but they are not persuasive.

Claim 2 provides for the use of an undefined chemical reagent to introduce a “phosphoramidite group” but, since the claim does not set forth any step(s) involved in the method/process, it is unclear what

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method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

5 In claim 3, adding a phosphoramidite-derivatized nucleoside to the terminus of a "growing" nucleic acid appears to make reference to the Caruthers process of nucleic acid synthesis, but remains incomplete for failure to specify the structural variables which define the complete chemical structural formula of the "phosphoramidite modified nucleoside."

10 Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

15 Claim 3 provides for the use of a 3'-phosphoramidite derivative of a 2'-modified nucleoside in a process wherein same is incorporated into an oligonucleotide but, since the claim does not set forth any step(s) involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

20 In claim 5, the term "nucleoside comprising a nucleoside analog" is indefinite because applicant has not provided adequate guidance within the instant claim or the instant disclosure to permit the ordinary practitioner to determine which compounds qualify as a "nucleoside analog" and which do not (an indefinite metes and bounds problem). In addition the newly added term "comprising" renders the entire term
25 technically inaccurate because the term "nucleoside" does not include the subject matter encompassed by the term "nucleoside analogue" and

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therefore, the latter included term cannot be fairly defined to be included within the former included term.

Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

5 Applicant is referred to the comments following the enablement and art rejections. Narrow claim language is necessary when referring to compounds. Compliance is respectfully requested.

10 In claim 8, the term "electron transfer moiety is a transition metal complex comprising a transition metal and at least one ligand" refers to both compounds and substituents, appearing to equate the two, a clear technical error. Said language also remains entirely functional including a term ("at least one") which lacks an upper bound, so examiner is unable to know what particular complex or complexes applicant is referring to or how said ligand(s) is/are modified for attachment to the resultant product. This error is further compounded by reliance
15 thereon by dependent claim 9.

Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

20 Applicant is referred to the comments following the enablement and art rejections. Narrow claim language is necessary when referring to compounds. Compliance is respectfully requested.

25 In claim 9, the term "wherein said transition metal complex comprises a transition metal selected from the group consisting of ruthenium, rhenium, osmium, platinum, cobalt and iron" is technically incorrect and incomplete because the structures of the "transition metal complex" must include other components than a metal or a metal ion;

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i.e. the complete structure of the implied ligand substituent. Applicant has therefore incompletely defined either the "transition metal complex" or the "electron transfer moieties" by failing to note in the claim all of the structural features intended to be included.

5 Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

Applicant is respectfully requested to completely define the subject matter to be claimed. Generic terminology and "comprising" does not adequately address this need.

10 Claim 10 contains nearly all of the same problems defined above for claim 7. The term "a covalently attached polydentate ligand" only hints at the structure of the intended product. Also said term is inconsistent with other terms in dependent claims 13 and 14 including "ferrocene" (not a substituent but a compound which includes an Fe^{+2} ion
15 coordinate-covalently bonded to two cyclopentadienyl anions) and "metallocene" (a name for the genus of organometallic compounds which includes ferrocene). As a consequence of these technical errors, claims 13 and 14 both lack proper antecedent basis in claim 10.

20 Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

Applicant is referred to the comments following the enablement rejection and the art rejection.

25 In claim 11, the term "the coordinating atom of said ligand" does not specify and therefore does not include a description of the overall structure of the ligand being claimed and is technically inaccurate (no ligand known to this examiner to be commonly in use relies on a single

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coordinating "atom"). Applicant appears to err when equating the noted term with the term "an organometallic ligand" as found in claims 13 and 14 because in claims 13 and 14 the exemplification indicated is not merely a ligand, but a complex of a ligand and a metal ion, aka an organometallic complex moiety.

Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

Applicant is referred to the comments following the enablement rejection and the art rejection.

In claim 13 the term "wherein said transition metal complex comprises an organometallic ligand and a metallocene" is incomplete because it is unclear what structural relationship exists between what appears to be a substituent ligand and a metallocene.

Applicant's arguments with respect to claims 2-11 and 13-15 have been considered but are moot in view of the new grounds of rejection.

Claims 2-11 and 13-15 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claims 2-11 and 13-15, the chemical reactants are described using generic terms only, thereby encompassing a substantial area of subject matter for which applicant has failed to provide adequate enabling support within the instant disclosure. Specifically terms such as "anhydro-nucleoside" (claim 1), and "nucleoside analog" (claim 5) is directed to a vast array of chemical structures while applicant's

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specification only discloses a limited number (one) of specific embodiments, leaving the ordinary practitioner the unreasonable burden of determining which claimed embodiments are actually operative and which are not (undue experimentation).

5 Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

10 Applicant argues that the disclosure must provide "... in light of the prior art ...ample guidance to one of skill in the art, to make and use the compounds of the invention." Examiner has inspected the sole example at pages 26-27, and has found that the description is extreme brief and lacks confirmatory spectral (^1H , NMR spectrum, ^{13}C NMR spectrum, mass spectrum, elemental analysis, etc.) data to permit confirmation of the asserted synthesis. Also, the acronyms DMTCl, DIEA and DBU are not defined. Examiner suspects that DMTCl is probably dimethoxytrityl
15 chloride, but is unfamiliar with the other acronym. Definitions of all three acronyms were not found by examiner elsewhere in the disclosure. Therefore, applicant has asserted broad coverage for a process, but as failed to provide even a single complete example to establish the minimum necessary credibility required for the ordinary practitioner to
20 practice the claimed process without undue experimentation. Additionally, at pages 26 and 27, last two paragraphs, it is unclear which particular chemical "product" is being referred to by the noted term in the noted paragraphs, where it appears that numerous intermediate "product[s]" are generated, but not identified by structure or referred to
25 by identifying character permitting correlation with the structures provided in the Schemes of Figures 1, 2 and 3. Also, at page 27, the term " CH_2Cl_2 " apparently is intended to refer to the solvent methylene chloride, aka
-- CH_2Cl_2 --. Applicant may address this rejection in part by amendment

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of the disclosure to include more complete descriptions of how to make all eight (8) chemical compounds shown in the Figure 3, with the assurance that this subject matter will not be the basis of the new matter rejection. As to the issue of scope, applicant's very minimal disclosure
5 does not justify broad claims in the instant case. If applicant wishes to obtain claims of broad scope (e.g. the generic "process for making a 2'-modified nucleoside"), a much more detailed and complete disclosure of several additional examples must be provided to show how parallel processes are carried out with much less synthetically forgiving
10 ribonucleoside starting materials (e.g. cytidine, adenosine and especially guanosine), a submission which would only be possible in a CIP application.

For these reasons, the instant grounds of rejection has been maintained.

15 The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

20 "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims 2-11 and 13-15 are rejected under 35 U.S.C. §103(a) as being unpatentable over Nexstar '102 (PTO-892 ref. L).

25 The instant claims are directed to a process for making labelled nucleosides from anhydro-nucleosides wherein the label is an "electron transfer moiety," for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling.

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The Nexstar '102 reference discloses processes for making labelled nucleosides from anhydro-nucleosides, for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling including compounds modified by metal-ion-containing coordination complexes (see pp. 9-10 and structure 1 at p. 9). Applicant is referred to pages 17, 21, 23, 26, 3140, 49, 50 and 53, and claim *1*, at p. 59, lines 10-11, and claims *5, 20, 22 and 25* wherein the last three claims disclose the nucleoside starting material, disclose the phosphoramidite analogues of the nucleoside, and imply the use of said phosphoramidites to make oligonucleotides incorporating the modified nucleosides by claiming compounds which could be the product of a phosphoramidite oligonucleotide synthesis.

Teachings of the prior art which disclose in detail subject matter which reads on the invention as claimed is deemed to render the instant claims lacking in patentable distinction in view of the noted prior art.

Therefore, the instant claimed process for making labelled nucleosides from anhydro-nucleosides, for making the phosphoramidites thereof, and for making standard or modified oligonucleotides or polynucleotides therefrom via phosphoramidite coupling, would have been obvious to one of ordinary skill in the art having the above cited reference before him at the time the invention was made.

Applicant's arguments filed November 6, 2001 have been fully considered but they are not persuasive.

Applicant argues that the instant rejection fails to establish a *prima facie* case of obviousness, asserting that the prior art reference "... does

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not teach the synthesis of nucleosides modified at the 2' position with a transition metal complex." Unfortunately, applicant does not specifically claim this noted subject matter either (the term "electron transfer moiety" covers a vast array of structures not all of which are metallic complexes), so the argument made is beside the point.

Examiner notes that the cited prior art covers a wide area with the term "fluorescent label" (see claim 35) which examiner interprets to overlap with the term "electron transfer moiety." Applicant may elect to avoid the prior art by using chemical structures in place of generic terminology to describe the 2'-substituent. As noted above (comments following enablement rejection), claims of very narrow scope are all that is supportable by the instant disclosure.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. §1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines
5 operated by Group 1600 are (703) 308-4556 and 703-305-3592.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-308-4639. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through
10 Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Johann Richter, can be reached at (703)-308-4532.

Any inquiry of a general nature or relating to the status of this
15 application should be directed to the Group 1600 receptionist whose telephone number is 703-308-1235.

LECrane:lec
20 05/22/02


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